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RESEARCH

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Evaluation of therapeutic potentials of some bioactive compounds in selected African plants targeting main protease (M^{pro}) in SARS-CoV-2: a molecular docking study

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Abstract

Background Coronavirus disease 2019 (COVID-19) is an infectious disease brought on by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a global treat in early 2020. Despite worldwide research proving different medications used to treat COVID-19, the infection still affects the human race; we need to continue researching the virus to protect humanity and reduce the complications that some medications might cause. This study focuses on finding another promising therapeutic compound against SARS-CoV-2. Twenty-four (24) bioactive compounds were selected from the following African plants' *Adansonia digitata L, Aframomum melegueta K. Schum, Ageratum conyzoides (L.) L*, and *Boswellia dalzielii, and* Remdesivir was used as the control medication. The PubChem web server acquired the 3D structures of bioactive compounds in the plant and the control medication. The SARS-CoV-2 main protease (M^{pro}) crystal structure was obtained using the Protein Data Bank (PDB). Using the SwissADME web server, the bioactive compounds' drug-likeness was assessed, and AutoDock was employed for the molecular docking with the M^{pro}. The Proteins Plus and Protein–Ligand Interaction Profiler web servers were used to analyse the docked complexes. Furthermore, the admetSAR website was utilized to predict the ligands' absorption, distribution, metabolism, excretion, and toxicity (ADMET) properties.

Results Based on the drug-likeness screening, Rutin violated more than one of the Lipinski rules of five, while Remdesivir violated two. Molecular docking analysis results indicated that Catechin, Epicatechin, Vitexin, Quercetin, Kaempferol, Gamma-Sitosterol, and Kaur-16-ene exhibited a stronger binding affinity with M^{pro}, with binding scores of − 7.1, − 7.1, − 8.0, − 7.3, − 7.2, − 6.8, and − 6.5 kcal/mol, respectively, compared to Remdesivir's binding score of − 6.3 kcal/mol. Consequently, binding scores of bioactive compounds suggest their potential biological activity against the SARS-CoV-2 main protease. Additionally, these bioactive compounds exhibited favourable ADMET properties. Vitexin also has a plasma protein binding below 90%, a promising medication distribution feature.

Conclusions This study shows that Catechin, Epicatechin, Vitexin, Quercetin, Kaempferol, Gamma-Sitosterol, and Kaur-16-ene have better binding affinities with M^{pro} than Remdesivir. Molecular dynamics simulation in vitro and in vivo investigation is required to support this study.

Keywords SARS-CoV-2, Main protease, Molecular docking

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Introduction

The acute respiratory illness known as Coronavirus Disease 2019 (COVID-19) is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1, 2]. Fever, coughing, tiredness, shortness of breathe, and odour loss are the most common COVID-19 signs. [3]. The virus is more contagious than earlier coronaviruses, although it has a lower mortality rate [4, 5]. As of April 2023, there have been 764.47 million confirmed cases and 6.9 million deaths, as the World Health Organization (WHO) reported. The development of therapies for COVID-19 patients has advanced. Several antiviral and immunomodulating medications are being tried, and protease inhibitors are also being considered prospective therapeutic targets because of their crucial function in the viral replication process [6]. These include using the SARS-CoV-2 replicate enzyme, in particular, encoding the main protease (M^{pro}) (also known as 3CLpro protease), which is conserved in all coronaviruses and is responsible for the cleavage of viral polyproteins [7, 8]. In October 2020, the FDA approved Remdesivir (also known as Veklury), marking a historic milestone as the first medication to treat COVID-19. Notably, this antiviral drug was discovered in 2016 to fight the Ebola virus infection common in Africa [9]. As demonstrated in other viral disorders, including acquired immunodeficiency syndrome, protease inhibitors and other medications may help battle treatment resistance. The urgency of finding new medications or novel uses for current medications to treat COVID-19 has been brought to light by the virus's quick proliferation and the dearth of viable treatments. Targeting the virus's main protease (M^{pro}), which is necessary for viral replication and is required for the virus to infect human cells, is one possible strategy.

Natural chemicals found in medicinal plants could be exploited as starting points for creating novel medications [10]. Natural products played a significant role in developing new medications to treat cancer, cardiovascular disease, multiple sclerosis, and infectious disorders [11]. Artemisinin from *Artemisia afra* and Cyclosporine from *Tolypocladium inflatum* are two examples of about 25% of medications that have been approved by the Food and Drug Administration (FDA) and the European Medical Agency (EMA); these medications are derived from plants [12].

Africa's diverse habitat and climate, including deserts, savannah, and tropical rainforests, cause the continent's rich flora [13]. According to Attah et al. (2021), phytomedicine and bioactive compounds derived from some African plants have been used in traditional medicine to exert antiviral, antibacterial, anti-inflammatory, and immunomodulatory effects [14]. The increased study of the world's biodiversity will allow bioactive compounds from plants to continue to play a significant part in alleviating global health-related diseases. In this study, we concentrated on four natural products associated with anti-inflammatory and antiviral effects [14]: *Adansonia digitata L, Aframomum melegueta K. Schum, Ageratum conyzoides,* and *Boswellia dalzielii Hutch.* To research whether these natural compounds could act as SARS-CoV-2 M^{pro} enzyme inhibitors, we conducted an in silico investigation.

The baobab tree (*Adansonia digitata L)* is a sizable African native deciduous tree [15]. The tree is frequently employed in conventional medicine to treat fever, diarrhoea, and respiratory infections. Plant parts, including leaves, bark, and fruit pulp, have long been utilized in many African nations as immunostimulants, anti-inflammatories, analgesics, insect repellents, and treatments for gastrointestinal infections [16].

Aframomum melegueta K. Schum, (*A. melegueta*) also called the alligator pepper, is a West African native and a member of the ginger family. It is a grown and natural tropical fruit that is peppery and edible. The seed of *A. melegueta* heals dysentery and acts as a sedative for toothaches, rheumatism, and migraines. It also has strong anti-inflammatory properties with a favourable gastrointestinal tolerance profile [17]. It has more powerful antibacterial action than Ampicillin, Gentamicin, and Vancomycin [18].

Ageratum conyzoides, also called Billy goat weeds, has a long history of use in traditional medicine in tropical and subtropical areas. Various diseases have been treated using *A. conyzoides* in Africa, Asia, and South America. In India, it is used as an oil lotion to treat leprosy and purulent ophthalmia. Numerous pharmacological properties of the phytoconstituents, including antibacterial, anti-inflammatory, analgesic, antioxidant, anticancer, antiprotozoal, antidiabetic, spasmolytic, and many more, have been proven [19, 20].

The frankincense tree, also known as *Boswellia dalzielii Hutch*, is an African-born tree. The tree's resin is widely used as traditional medicine to cure some ailments, such as respiratory infections, inflammation, and discomfort. Its pharmacological activities have been revealed in some research, which includes antibacterial [21, 22], anti-inflammatory [23], anti-HIV/AIDS [24], and anticancer effects [25].

Given the observed antiviral and anti-inflammatory effects, bioactive compounds from the above plants may be therapeutic against SARS-CoV-2. We used *an* in silico approach to look into these bioactive compounds' potential as M^{pro} enzyme inhibitors. In silico analysis is a computational technique that predicts the binding affinity between a ligand and a protein target. This method can be applied to rapidly and accurately discover

potential medication candidates. In this study, we used AutoDock, a well-known molecular docking program, to predict the binding affinity between the natural products from four African plants (*Adansonia digitata L, Aframomum melegueta K. Schum, Ageratum conyzoides (L.) L*, and *Boswellia dalzielii Hutch*) and the M^{pro} enzyme of SARS-CoV-2. The findings of this investigation will provide insights into the potential of these bioactive compounds as SARS-CoV-2 M^{pro} enzyme inhibitors. New medications for the treatment of COVID-19 may be created due to the study's findings.

Materials and methods

Ligands selections and preparations

Twenty-four (24) bioactive compounds (Ligands) from four African plants (*Adansonia digitata L* [26], *Aframomum melegueta K. Schum*. [27], *Ageratum conyzoides (L.) L* [28], and *Boswellia dalzielii Hutch* [29]) are obtained from literature based on therapeutic potential and unique properties of the plants, such as their antiviral property. The control medication used in this study was Remdesivir. The PubChem web server (https://pubchem.ncbi.nlm.nih.gov/) [30] was utilized to acquire the Simplified Molecular Input Line Entry System (SMILES), the 3D structure in Structure Data Format (SDF), and the PubChem identification number (PID) for both the bioactive compounds and the control medication. These details were necessary for conducting the in silico analysis. Table 1 presents bioactive compounds from the aforementioned African plants and the control medication. Figure 1 presents the flow chart of the study.

Protein target selection

The main protease (M^{pro}) identified in SARS-CoV-2 with Protein Data Bank (PID) number 6lu7 was used as the target protein in this study. The protein data bank (http://www.rcsb.org) maintained by the Research Collaboratory of Structural Bioinformatics (RCSB) [31], a widely used database, was used to obtain the three-dimensional (3D) crystallographic structure of this target protein. The Main Protease (M^{pro}) of the SARS-CoV-2 is depicted graphically in Fig. 2.

Table 1 Lipinski's drug-likeness screening of the bioactive compounds and the control medication

S/N	Plants	Bioactive compounds	Chemical formulae	Molecular weight	LogP	Number of HB acceptor	Number of HB donor	No. of violation
1	*Adansonia digitata L*	Catechin	$C_{15}H_{14}O_6$	290.27	0.36	6	5	0
		Epicatechin	$C_{15}H_{14}O_6$	290.27	0.36	6	5	0
		Vitexin	$C_{21}H_{20}O_{10}$	432.38	0.21	10	7	1
		Quercetin	$C_{15}H_{10}O_7$	302.24	1.54	7	5	0
		Kaempferol	$C_{15}H_{10}O_6$	286.24	1.90	6	4	0
		Rutin	$C_{27}H_{30}O_{16}$	610.52	− 0.33	16	10	3
2	*Aframomum melegueta K. Schum*	n-Hexadecanoic acid	$C_{16}H_{32}O_2$	256.42	7.17	2	1	1
		Corymbolone	$C_{15}H_{24}O_2$	236.35	2.98	2	1	0
		Gamma-Sitosterol	$C_{29}H_{50}O$	414.71	9.34	1	1	1
		Myrtenyl acetate	$C_{12}H_{18}O_2$	194.27	3.79	2	0	0
		Gamma-Muurolene	$C_{15}H_{24}$	204.35	4.31	0	0	1
		Isonicotinic acid	$C_6H_5NO_2$	123.11	0.32	3	1	0
3	*Ageratum conyzoides (L.) L*	Azulene	$C_{10}H_8$	128.17	3.2	0	0	0
		Norfenefrine	$C_8H_{11}NO_2$	153.18	− 0.82	3	3	0
		Kaur-16-ene	$C_{20}H_{32}$	272.47	6.91	0	0	1
		2-Acetylcyclopentanone	$C_7H_{10}O_2$	126.15	0.35	2	0	0
		Alpha-Calacorene	$C_{15}H_{20}$	200.32	4.41	0	0	1
		Longipinocarveol, trans	$C_{15}H_{24}O$	220.35	3.85	1	1	0
4	*Boswellia dalzielii Hutch*	Lavandulol	$C_{10}H_{18}O$	154.25	3.02	1	1	0
		Cyperene	$C_{15}H_{24}$	204.35	4.32	0	0	1
		Aromadendrene	$C_{15}H_{24}$	204.35	4.71	0	0	1
		Viridiflorol	$C_{15}H_{26}O$	222.37	3.74	1	1	0
		Cis-Chrysanthemol	$C_{10}H_{18}O$	154.25	2.52	1	1	0
		Beta-Phellandrene	$C_{10}H_{16}$	136.23	3.44	0	0	0
	Control medication	Remdesivir	$C_{27}H_{35}N_6O_8P$	602.58	1.91	12	4	2

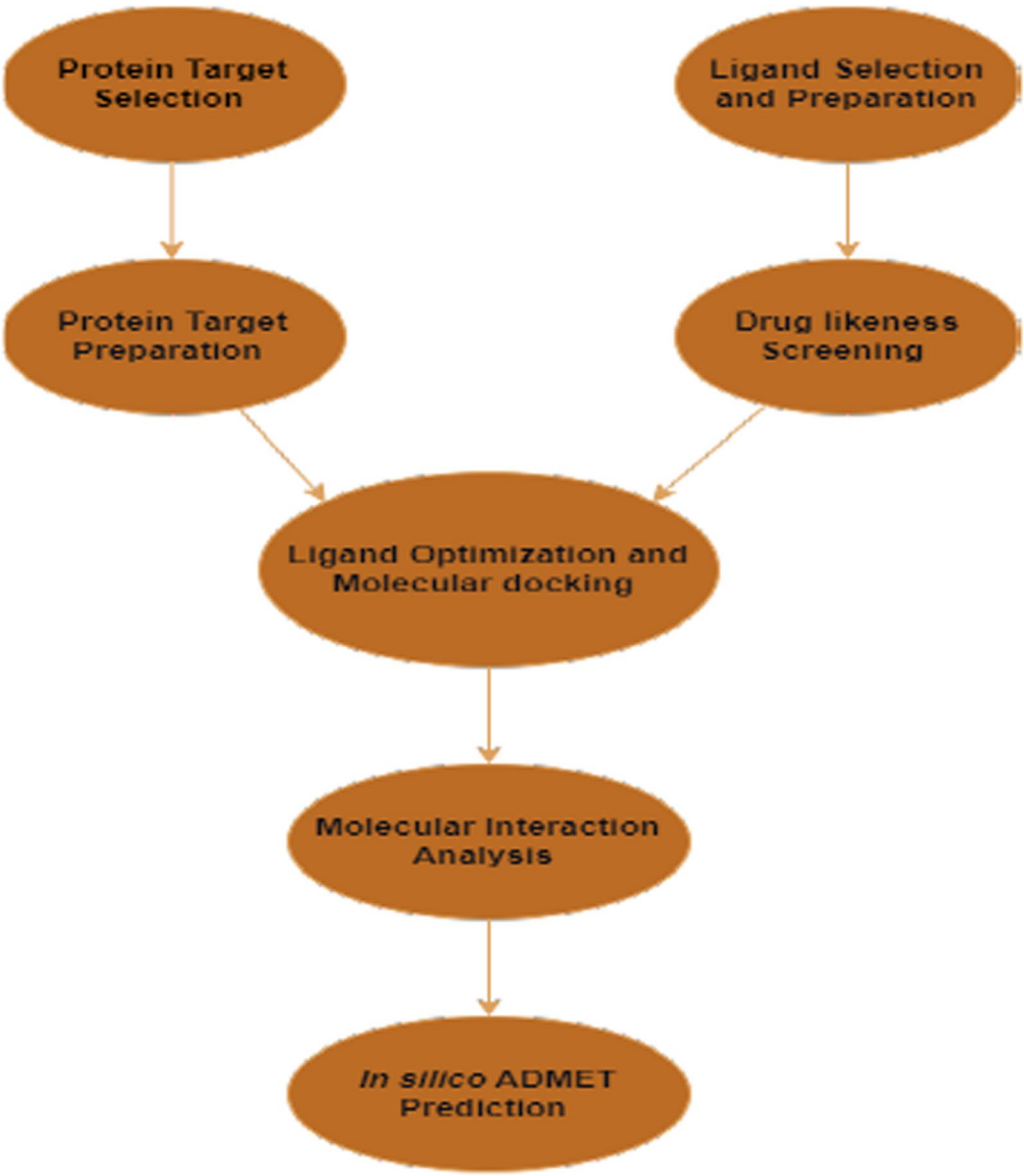

Fig. 1 Flow chart of the study

Protein target preparation

The 3D structure of the target protein obtained for the Protein Data Bank (PDB) was prepared and cleaned using the UCSF-Chimera (version 1.13.1) software [32]. The protein was cleaned by eliminating the co-crystallized ligand and any accompanying water molecules, resulting in a refined receptor. Hydrogen charges were subsequently added to the protein, and it was further subjected to minimization for molecular docking purposes. Finally, the prepared protein structure was saved in PDB format.

Drug-likeness screening

The bioactive compounds obtained for the four plants and the control medication are subjected to drug-likeness screening. We used the SwissADME online web server (http://swissadme.ch/) [33] for the screening. The Simplified Molecular Input Line Entry System (SMILES) of bioactive compounds and the control medication, obtained from the PubChem online web server, were utilized for the screening process. Lipinski's rule of five [34] was applied as a criterion to identify potential oral medication candidates. In our study, any bioactive compounds

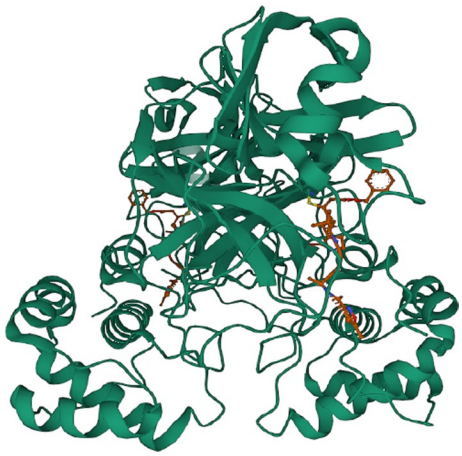

Fig. 2 The crystal structure of SARS-CoV-2 M^{pro} in complex with N3. [2, 34]. Adopted from protein data bank

that violated only one out of Lipinski's rule of five were subjected to molecular docking.

Ligands optimizations and molecular docking

The Python prescription (PyRx) software [35], which contained the Autodock, was used for the molecular docking of bioactive compounds and the target protein to predict the binding affinity. The Open Babel integration within PyRx (version 0.8) was employed to optimize the ligands and prepare them for docking. The 3D structure of the downloaded bioactive compounds and the control medication were uploaded into the software for molecular docking. Subsequently, the ligands were converted to the AutoDock ligand format Protein Data Bank, Partial Charge (Q), and Atom Type (T) (PDBQT). The molecular docking was carried out using AutoDock. To define the protein's active site, a grid box was adjusted with specific dimensions (x: 17.9373, y: 8.5847, z: 63.4097) and size (x: 105.5044, y: 131.7599, z: 92.1029 angstroms). The following amino acids were selected from literature [2, 36] and used for the molecular docking process; Thr25, Cys44, Thr26, His41, Met49, Tyr54, Phe140, Leu141, Gly143, Cys145, Asn142, His163, His164, Met165, Ser144, Glu166, Pro168, His172, Val186, Asp187, Arg188, Gln189, Phe185, Thr190, and Gln192.

Molecular interaction analysis

A graphical user interface (GUI) software called PyMOL© molecular graphics (version 2.4, 2010, Schrödinger LLC) [37] was used for protein–ligand complex formation and the molecular interaction of the ligands. The complexes generated were saved in PDB format and stored for further analysis. The molecular interactions of the complexes are analysed using Protein–Ligand Interaction Profiler (https://plip-tool.biotec.tu-dresden.de/plip-web/plip/index) [38] and Proteins Plus online server (https://proteins.plus) [39, 40].

Prediction of in silico ADMET properties

The bioactive compounds derived from the molecular docking, which exhibited more remarkable binding affinities than the control medication, were assessed for their absorption, distribution, metabolism, excretion, and toxicity (ADMET) properties. This evaluation was performed using the admetSAR web server (http://lmmd.ecust.edu.cn/admetsar2/) [41]. The results obtained from this analysis were then utilized to predict the pharmacokinetic characteristics of bioactive compounds.

Results

Drug-likeness screening of selected bioactive compounds

Identifying the biological features of medication candidates through drug-likeness screening is crucial in discovering and developing new medications. The SwissADME online web server was used to evaluate the drug-likeness properties of 24 bioactive compounds from four African plants and the control medication (Table 1). From the screening, 23 bioactive compounds only violated at most one violation out of Lipinski's rule of five. Remdesivir, the control medication, has two violations of the Lipinski rules. However, Rutin has three violations of the Lipinski rules; hence, it was eliminated from the study for further analysis.

Molecular docking and interaction of bioactive compounds with SARS-CoV-2 Main protease (M^{pro})

The catalytic site of M^{pro} is comprised of specific amino acid residues, namely Thr25, Cys44, Thr26, His41, Met49, Tyr54, Phe140, Leu141, Gly143, Cys145, Asn142, His163, His164, Met165, Ser144, Glu166, Pro168, His172, Val186, Asp187, Arg188, Gln189, Phe185, Thr190, and Gln192 [2, 36]. Table 2 presents the results of the molecular docking analysis conducted in this study, which reveals the binding affinity, electrostatic energy, hydrophobic interactions, π-stacking interactions, and hydrogen bond interactions between bioactive compounds and M^{pro}.

The findings in Table 2 demonstrate the potential biological activity of bioactive compounds derived from the four African plants against the target protein, M^{pro}, along with their predicted binding affinities. *Adansonia digitata L* contains Catechin, Epicatechin, Vitexin, Quercetin, and Kaempferol as bioactive compounds. The molecular docking results indicate that Catechin, Epicatechin, Vitexin, Quercetin, and Kaempferol bind to the target protein, M^{pro}, with binding energies of − 7.1, − 7.1, − 8.0, − 7.3, and − 7.2 kcal/mol, respectively. Among these compounds, Vitexin exhibits the highest binding

Table 2 Analysis of molecular interactions for the bioactive compounds and the control medication

S/N	Plant source	Bioactive compounds	Binding energy (kcal/mol)	Number of hydrogen bond (s) formed	Residues involved in hydrogen bond formation (Å)	Residues involved in hydrophobic interaction (Å)	Residues involved in π-stacking (Å)
1	*Adansonia digitata L*	**Catechin**	− 7.1	6	Ser144(2.32,2.34) His163(2.32) Glu166(3.36,2.74) Asp187(3.35	Met165(3.47) Gln189(3.87)	
		Epicatechin	− 7.1	5	Thr26(3.34,1.93) Tyr54(3.67,3.44) Gly143(2.51)	Met165(3.39) Gln189(3.68)	His41(4.81)
		Vitexin	− 8.0	3	Asp187(2.15) Gln189(2.78) Thr190(2.68)	His41(3.88) Glu166(3.61) Gln189(3.86)	
		Quercetin	− 7.3	4	Phe140(2.71) Thr190(3.22,2.04) Gln192(2.84	Met165(3.72) Glu166(3.03) Gln189(3.98)	
		Kaempferol	− 7.2	6	Thr26(2.22) Gly143(2.19) Ser144(3.11,2.28) Cys145(2.37) His163(3.13)	Glu166(3.86)	
	Aframomum melegueta K. Schum	n-Hexadecanoic acid	− 3.8	1	Gly275(2.03)	Phe223(3.73) Glu270(3.37) Leu271(3.63)	
		Corymbolone	− 5.6	3	Phe219(2.33) Arg279(2.79,2.67)	Glu270(3.59,3.66)	
		Gamma-Sitosterol	− 6.8	–		Val104(3.88,3.45) Ile106(3.82) Ile249(3.68) Phe294(3.62,3.41,3.50,3.94)	
		Myrtenyl acetate	− 5.1	–		Trp218(3.60) Glu270(3.36) Leu271(3.52) Asn274(3.79)	
		Gamma-Muurolene	− 5.7	–		Thr199(3.80) Tyr237(3.58) Leu272(3.72) Leu286(3.67) Leu287(3.68,3.86)	
		Isonicotinic acid	− 4.3	2	Asn221(2.70) Gly275(2.37)	Glu270(3.74)	
	Ageratum conyzoides (L.) L	Azulene	− 5.6	-		Trp218(3.69) Asn221(3.68) Phe223(3.79) Glu270(3.70,3.69) Leu271(3.45)	
		Norfenefrine	− 4.8	4	Gly15(1.89) Gly71(2.63) Asn95(2.92) Gly120(2.53)	Trp31(3.92)	Lys97(4.64)
		Kaur-16-ene	− 6.5	–		Trp218(3.60) Arg222(3.77) Glu270(3.73) Asn274(3.74)	
		2-Acetylcyclopentanone	− 4.3	2	Arg279(2.90,2.39)	Glu270(3.69) Asn274(3.78)	
		Alpha-Calacorene	− 5.8	–		Tyr239(3.50) Leu286(3.67) Leu287(3.80,3.73)	
		Longipinocarveol, trans-	− 6.2	2	Lys102(2.83) Ser158(2.16)	Asp153(3.75) Phe294(3.72,3.85,3.68)	

Table 2 (continued)

S/N	Plant source	Bioactive compounds	Binding energy (kcal/mol)	Number of hydrogen bond (s) formed	Residues involved in hydrogen bond formation (Å)	Residues involved in hydrophobic interaction (Å)	Residues involved in π-stacking (Å)
	Boswellia dalzielii Hutch	Lavandulol	– 4.4	3	Phe219(1.84) Asn221(3.56) Leu271(3.57)	Asn221(3.66) Phe223(3.61) Glu270(3.72) Asn274(3.69)	
		Cyperene	– 6.1			Trp218(3.75) Asn221(3.71) Phe223(3.60) Glu270(3.89,3.60) Leu271(3.58) Asn274(3.86)	
		Aromadendrene	– 6.1			Phe8(3.81) Val104(3.61) Ile106(3.68) Gln110(3.79) Asp153(3.93) Phe294(3.52,3.52)	
		Viridiflorol	– 6.0	1	Gln110(2.06)	Val104(3.86) Ile106(3.68) Gln110(3.39) Asn151(3.64) Phe294(3.95,3.65,3.76,3.89)	
		Cis-Chrysanthemol	– 4.4	–	–	Phe3(3.31) Lys5(3.68) Leu282(3.84) Glu288(3.56) Phe291(3.90,3.96)	
		Beta-Phellandrene	– 4.5	–		Phe3(3.56) Leu282(3.38) Glu288(3.75) Phe291(3.57)	
		Remdesivir	– 6.3	8	Arg131(3.02,2.69) Lys137(2.60) Thr199(1.92) Tyr237(3.41) Tyr239(2.93) Leu287(1.99) Asp289(1.93)	Tyr237(3.60) Leu272(3.70) Leu286(3.71,3.81) Leu287(3.47)	

Compounds in bold letters are the best-hit ligands

affinity. The binding and molecular interactions between the bioactive compounds and target protein are depicted in Fig. 3a–e.

The bioactive compounds present in *Aframomum melegueta K. Schum* consist of n-Hexadecanoic acid, Corymbolone, Gamma-Sitosterol, Myrtenyl acetate, Gamma-Muurolene, and Isonicotinic acid. These compounds exhibit binding energies of − 3.8, − 5.6, − 6.8, − 5.1, − 5.7, and − 4.3 kcal/mol, respectively, when interacting with M^{pro}. Among them, Gamma-Sitosterol demonstrates the highest affinity for binding to M^{pro}. The interactions of n-Hexadecanoic acid, Corymbolone, Gamma-Sitosterol, Myrtenyl Acetate, Gamma-Muurolene, and Isonicotinic Acid with M^{pro} are depicted in Fig. 4a–f.

The bioactive compounds identified in *Ageratum conyzoides (L.) L.* consist of Azulene, Norfenefrine, Kaur-16-ene, 2-acetylcyclopentanone, Alpha-calacorene, and Longipinocarveol, trans. Their binding energies to M^{pro} are − 5.6, − 4.8, − 6.5, − 4.3, − 5.8, and − 6.2 kcal/mol. The interactions of these compounds with the target protein are illustrated in Fig. 5a–f. Among them, Kaur-16-ene demonstrates the highest binding affinity to the target protein.

Bioactive substances found in *Boswellia dalzielii Hutch* include Lavandulol, Cyperene, Aromadendrene, Viridiflorol, Cis-chrysanthemol, and Beta-phellandrene. The molecular docking results show that Lavandulol, Cyperene, Aromadendrene, Viridiflorol, Cis-Chrysanthemol, and Beta-Phellandrene binds with the target

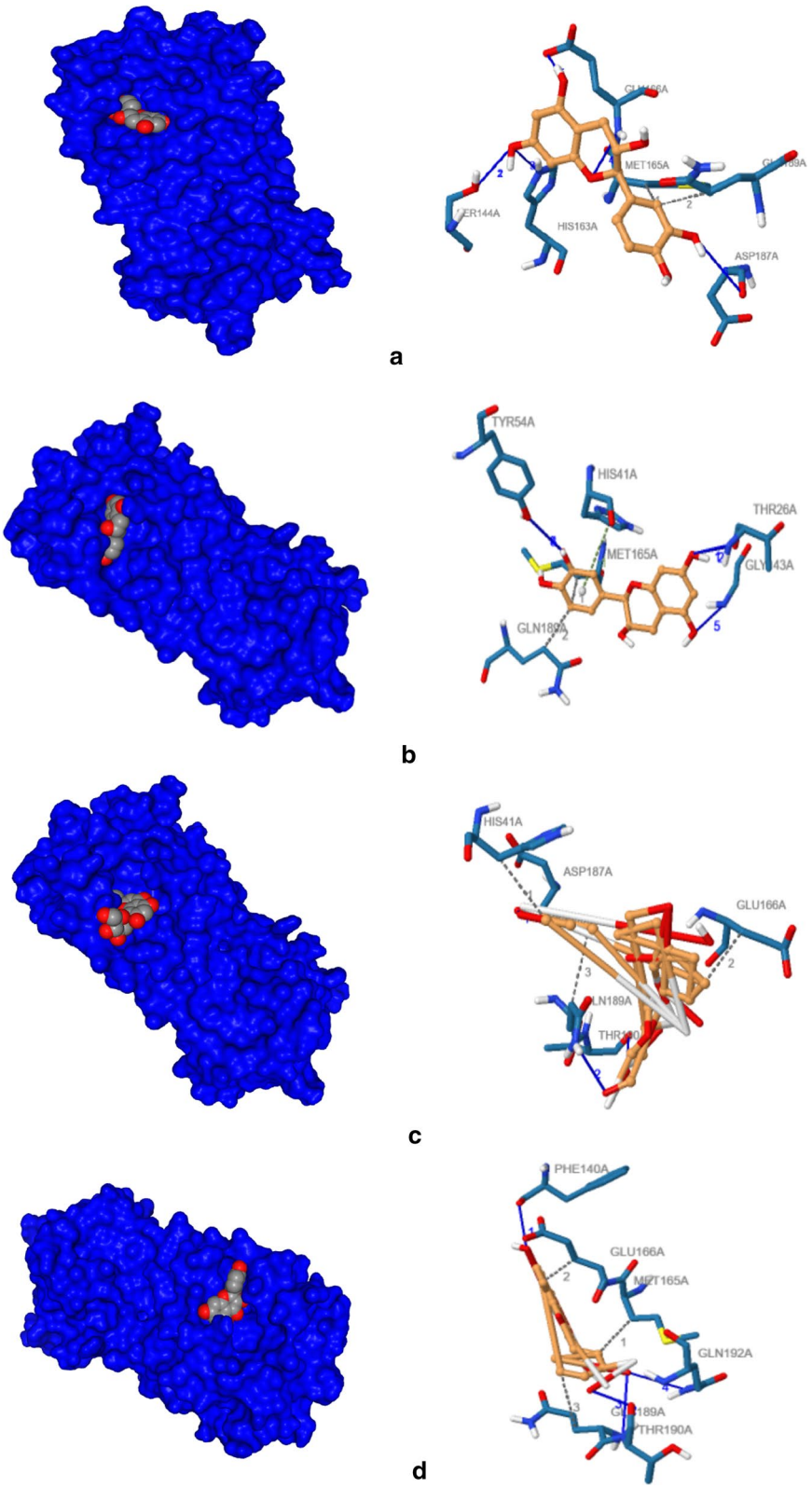

Fig. 3 The binding arrangement of Catechin (**a**), Epicatechin (**b**), Vitexin (**c**), Quercetin (**d**), and Kaempferol (**e**) in the active site of the M^{pro} as obtained from molecular docking using AutoDock. The Protein–Ligand Interaction Profiler and Proteins Plus online service were employed to evaluate the binding interactions. Hydrogen bonds are depicted by blue dashed lines, pi stacking by green, and hydrophobic interactions by grey

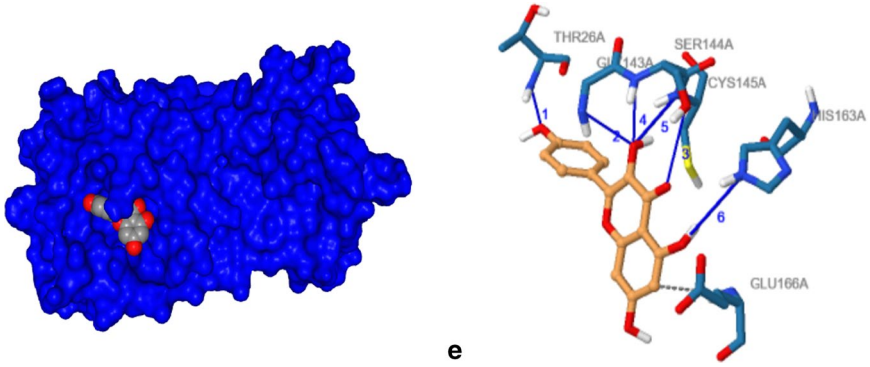

Fig. 3 continued

protein (M^{pro}) with binding energies of − 4.4, − 6.1, − 6.1, − 6.0, − 4.4, and − 4.5 kcal/mol, respectively. Cyperene and Aromadendrene have the highest binding affinity out of the six bioactive compounds. Figure 6a–f depicts bioactive compounds' binding and molecular interaction with the target protein.

The control medication in this study, Remdesivir, has a binding energy of − 6.3 kcal/mol. Figure 7 depicts the binding and molecular interaction of Remdesivir with M^{pro}.

In silico ADMET properties

Table 3 presents the predicted ADMET profiles of the bioactive compounds derived from four African plants and the control medication investigated in this study. Regarding absorption properties, Kaempferol, Gamma-Sitosterol, and Kaur-16-ene exhibit superior Caco-2 permeability compared to the other compounds, with values exceeding − 5.15 log cm/s. None of the identified ligands or the control medication demonstrates P-glycoprotein (Pgp) inhibition. Concerning distribution property, only Vitexin and the control medication display a plasma protein binding below 90%. Except for Gamma-Sitosterol and Kaur-16-ene, all the identified ligands and the control medication are predicted to be unable to cross the blood–brain barrier (BBB) (Fig. 8).

All bioactive compounds, except Kaur-16-ene, are not anticipated to be subject to CYP2D6 metabolism when it comes to medicine metabolism features. Among the hit ligands, Kaempferol and Quercetin exhibit inhibition of CYP1A2, suggesting a potential inhibition of liver metabolism. Except for Gamma-Sitosterol and Kaur-16-ene, all other compounds and the control medication are likely to be substrates for CYP3A4. Additionally, Kaempferol is predicted to inhibit CYP3A4. Regarding toxicity properties, only Remdesivir inhibits the human ether-a-go-go-related gene and is also associated with potential hepatotoxicity in humans. None of the compounds, including the control medication, are predicted to be carcinogenic.

Discussion

In silico drug research methodologies are crucial for identifying effective treatment options for diseases and infections of global health concern, thus playing a more significant role in drug discovery and development. These computational techniques have been used to suggest numerous compounds and molecules, and some predicted molecules have been used to treat COVID-19 [42]. This study sought to investigate further potential natural compounds that will be used in managing COVID-19 with little or no side effects. We selected twenty-four (24) bioactive compounds from four African plants, *Adansonia digitata L, Aframomum melegueta K. Schum, Ageratum conyzoides (L.), and Boswellia dalzielii Hutch*.

The bioactive compounds derived from four African plants were subjected to molecular docking against the main protease (M^{pro}) found in SARS-CoV-2, with Remdesivir as the reference medication. The PyRx software was utilized to determine the binding affinities of bioactive compounds with the target protein M^{pro}. Furthermore, a web-based application was employed to predict the pharmacokinetic properties of these bioactive substances. Our study assessed the drug-likeness characteristics of bioactive compounds and the control medication by applying Lipinski's rule of five. Lipinski's rule of five, which considers a medication's biological and pharmacological properties, helps determine a compound's potential effectiveness as an orally administered medication.

After the screening process, a total of twenty-three (23) compounds were identified that either complied with Lipinski's rule of five or had only one violation, except for Rutin and the control medication Remdesivir, which had three and two violations, respectively, as indicated in Table 1. Among the twenty-three (23) bioactive compounds with 0 or 1 violation, excluding Rutin

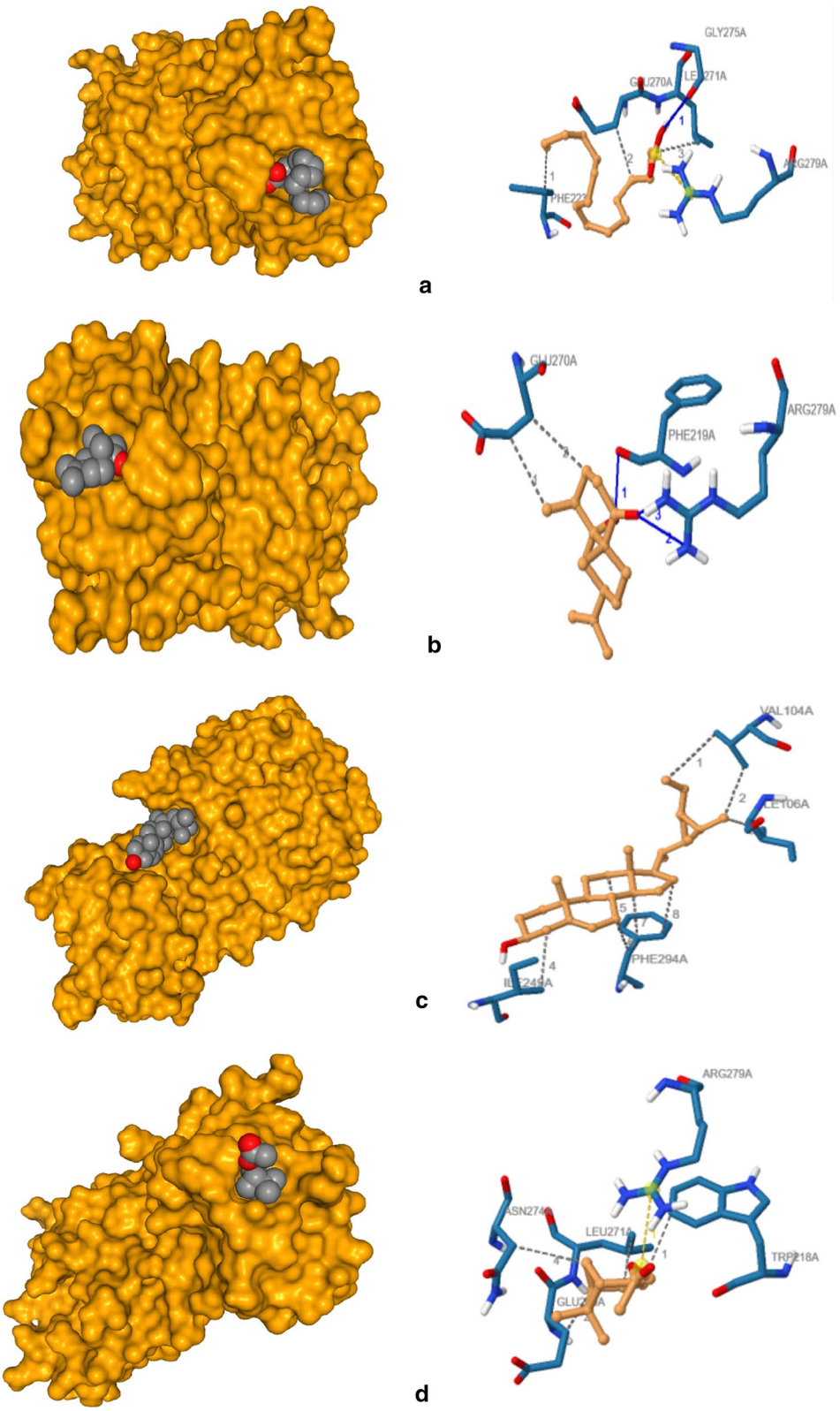

Fig. 4 The binding arrangement of n-Hexadecanoic acid (**a**), Corymbolone (**b**), Gamma-Sitosterol (**c**), Myrtenyl acetate (**d**), Gamma-Muurolene (**e**) and Isonicotinic Acid (**f**) in the active site of the M^{pro} as obtained from molecular docking using AutoDock. The Protein–Ligand Interaction Profiler and Proteins Plus online service were employed to evaluate the binding interactions. Hydrogen bonds are depicted by blue dashed lines, pi stacking by green, and hydrophobic interactions by grey

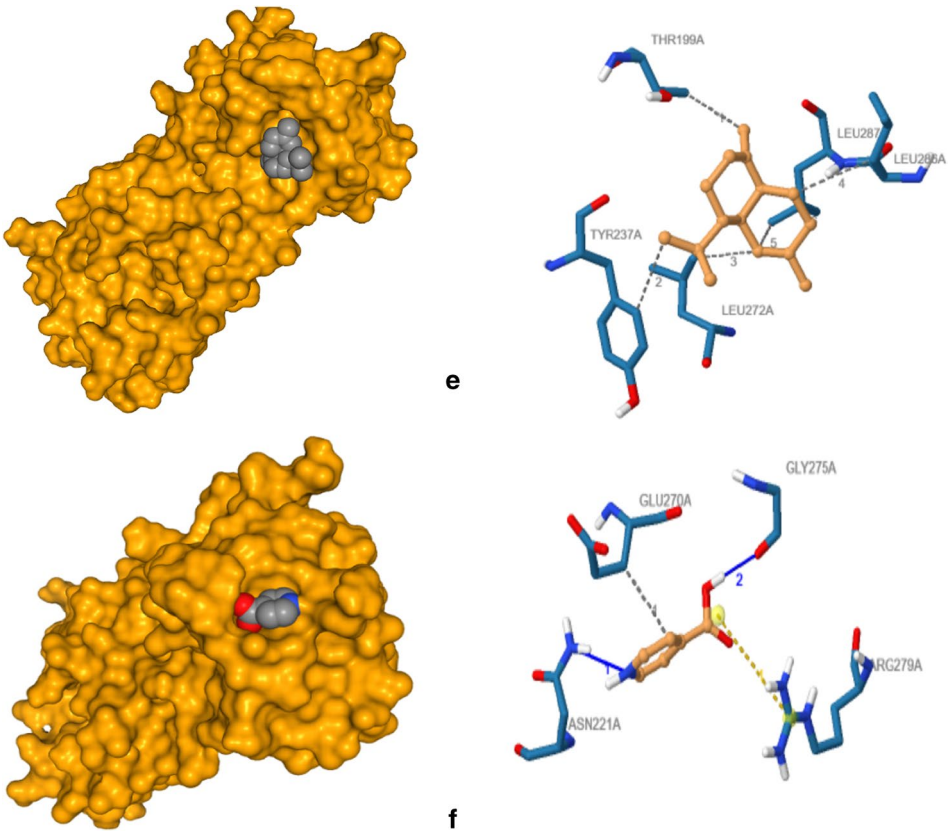

Fig. 4 continued

and Remdesivir, their molecular weights are within the Lipinski range (≤500 Daltons). According to Lipinski's rule of five, a medication with a molecular weight of 500 Daltons or less possesses favourable druggability and can be utilized as a drug [43]. It is worth noting that the molecular weight of medications also impacts their therapeutic potential. The compound's surface area increases once the molecular weight surpasses a certain threshold, decreasing penetrability [44]. Following this rule, the twenty-three (23) bioactive compounds investigated in our study can be utilized as oral medications without compromising their penetrability. Another aspect of Lipinski's rule of five suggests that a therapeutic compound favours hydrophobic (non-polar) environments if LogP > 5 and hydrophilic (polar) environments if LogP < 5 [43]. The results obtained from this study demonstrate that 21 bioactive compounds, including the control medication, have LogP values below 5, indicating favourable interactions in the polar environment of amino acids. Conversely, three bioactive compounds have LogP values exceeding 5, suggesting favourable interactions in non-polar environments.

The target protein (M^{pro}) was docked against the 23 bioactive compounds from four African plants as part of this study's molecular docking evaluation using PyRx software. M^{pro}, found in SARS-CoV-2, is a cysteine protease whose structure depicts a homodimer consisting of two protomers with a specific substrate-binding site. The substrate-binding site consists of cysteine and histidine amino acids (His41 and Cys145) that control the catalytic activity of SARS-CoV-2 [45].

M^{pro} has been validated as the protein target for promising natural compounds to interact with and enable the development of medications for COVID-19 because of the vital role it plays in SARS-CoV-2 replication and the production of polypeptide synthases inside the host, as well as the fact that no homolog of the protein can be found in humans [46]. As shown in Table 2, the docking analysis revealed that Catechin, Epicatechin, Vitexin, Quercetin, and Kaempferol are some of the bioactive compounds in *Adansonia digitata. L* has a better binding affinity with the protein target than Remdesivir. Vitexin had the best binding affinity of − 8.0kcal/mol, followed by Quercetin with a binding score of − 7.3kcal/mol.

Kaempferol also had an excellent binding score of − 7.2kcal/mol, and Catechin and Epicatechin had the same binding score of − 7.1kcal/mol. Gamma-Sitosterol, one of the bioactive compounds in *Aframomum*

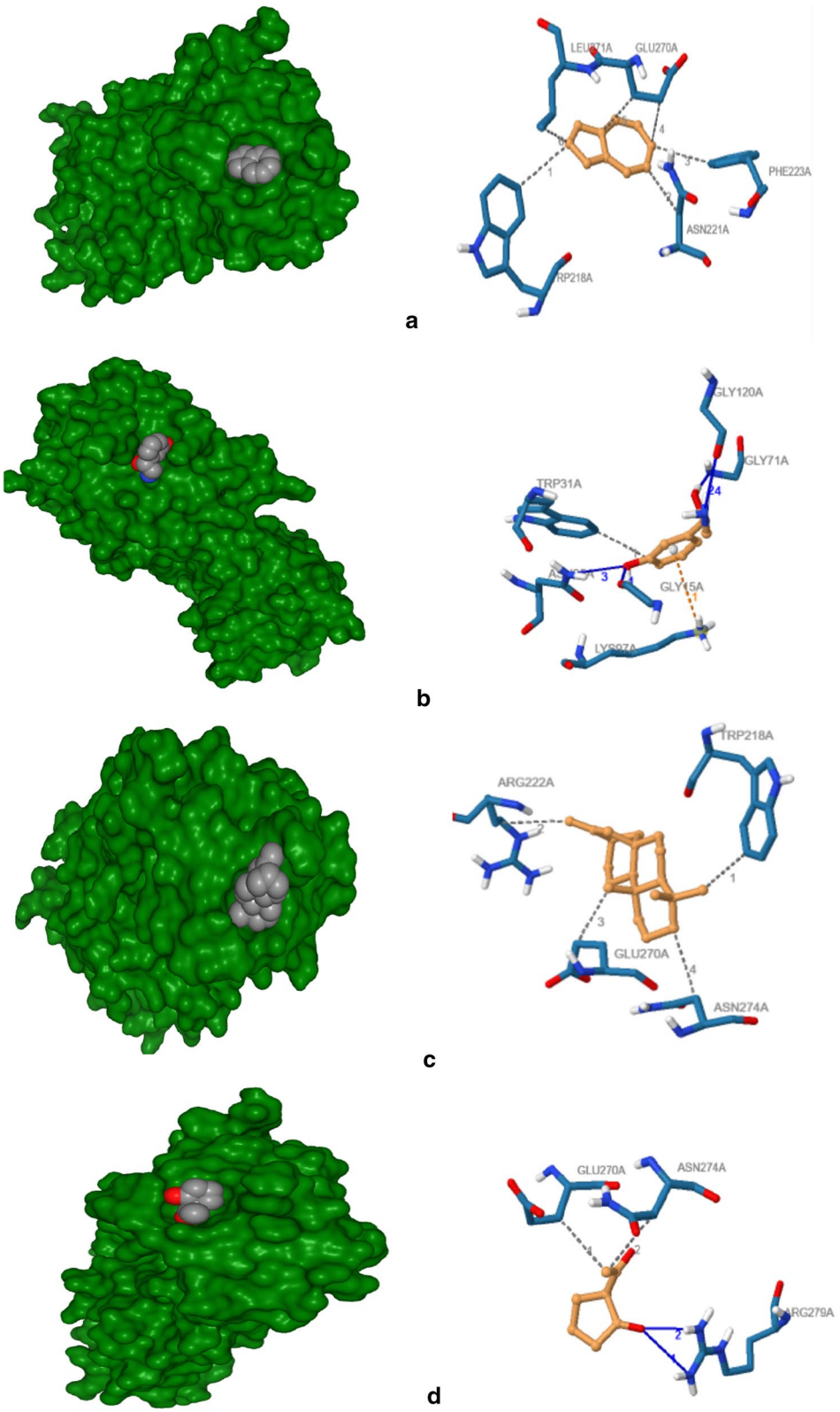

Fig. 5 The binding arrangement of Azulene (**a**), Norfenefrine (**b**), Kaur-16-ene (**c**), 2-Acetylcyclopentanone (**d**), Alpha-Calacorene (**e**) and Longipinocarveol, trans- (**f**) in the active site of the M^{pro} as obtained from molecular docking using AutoDock. The Protein–Ligand Interaction Profiler and Proteins Plus online service were employed to evaluate the binding interactions. Hydrogen bonds are depicted by blue dashed lines, pi stacking by green, and hydrophobic interactions by grey

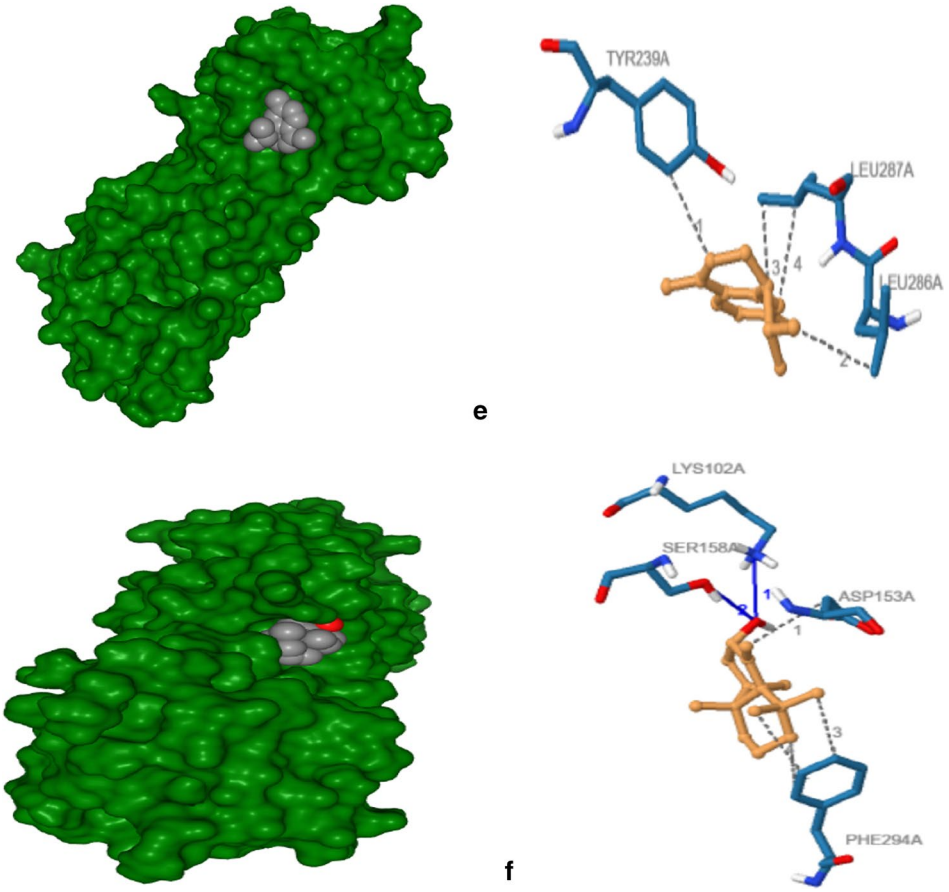

Fig. 5 continued

melegueta K. Schum, showed a better binding affinity with the protein target, with a score of − 6.8kcal/mol. Another compound in our study is Kaur-16-ene, a bioactive compound from *Ageratum conyzoides (L.) L*, also exhibited an excellent binding mechanism with the protein target, with a score of − 6.5kcal/mol. These seven compounds exhibited better binding mechanisms with the protein target than the control medication. The molecular docking method estimates compounds' optimal binding conformation within the protein binding pocket and the interaction between the ligand and the protein's active site [47]. In this study, in silico research suggests that Catechin, Epicatechin, Vitexin, Quercetin, Kaempferol, Gamma-Sitosterol, and Kaur-16-ene can inhibit the catalytic activities of M^{pro} by binding to the active site of the protein and interacting hydrophobically with the amino acid located deeper inside the protein, thereby denaturing it, which consequently inhibits the replication of SARS-CoV-2 and the production of polypeptide synthases inside the host. Hence, these compounds may offer antiviral benefits in treating COVID-19. Corresponding research that aligns with our finding is the research on the effect of Catechin on influenza infection in a randomized controlled trial, which indicates the anti-infective properties of Catechin and the use of Catechin as an effective prophylaxis against the viral infection [48]. Another literature review by Reygaert (2018) [49] also reiterates the antimicrobial and antiviral properties of Catechin and Epicatechin, which have the potential to inhibit viral RNA and DNA synthesis, inhibit viral gene transcription, and destroy various functional viral molecules [50, 51].

Additionally, an in vitro and *in silico* study by Fahmy et al. (2020) [52] found that Vitexin had high antiviral activity against the HAV-H10 and HSV-1 viruses, and it came to the conclusion that Vitexin is a possible natural molecule that can be used in the development of antiviral medications [53]. Another study corresponding to our findings is the in vivo and in vitro study on Kaempferol, which revealed its ability to reduce Herpes simplex virus encephalitis (HSE) by inhibiting the secretion of microglial pro-inflammatory factors and inducing apoptosis of microglia cells [54]. Consistent with our study is also the research by Ferrao and Janeque (2023) [55],

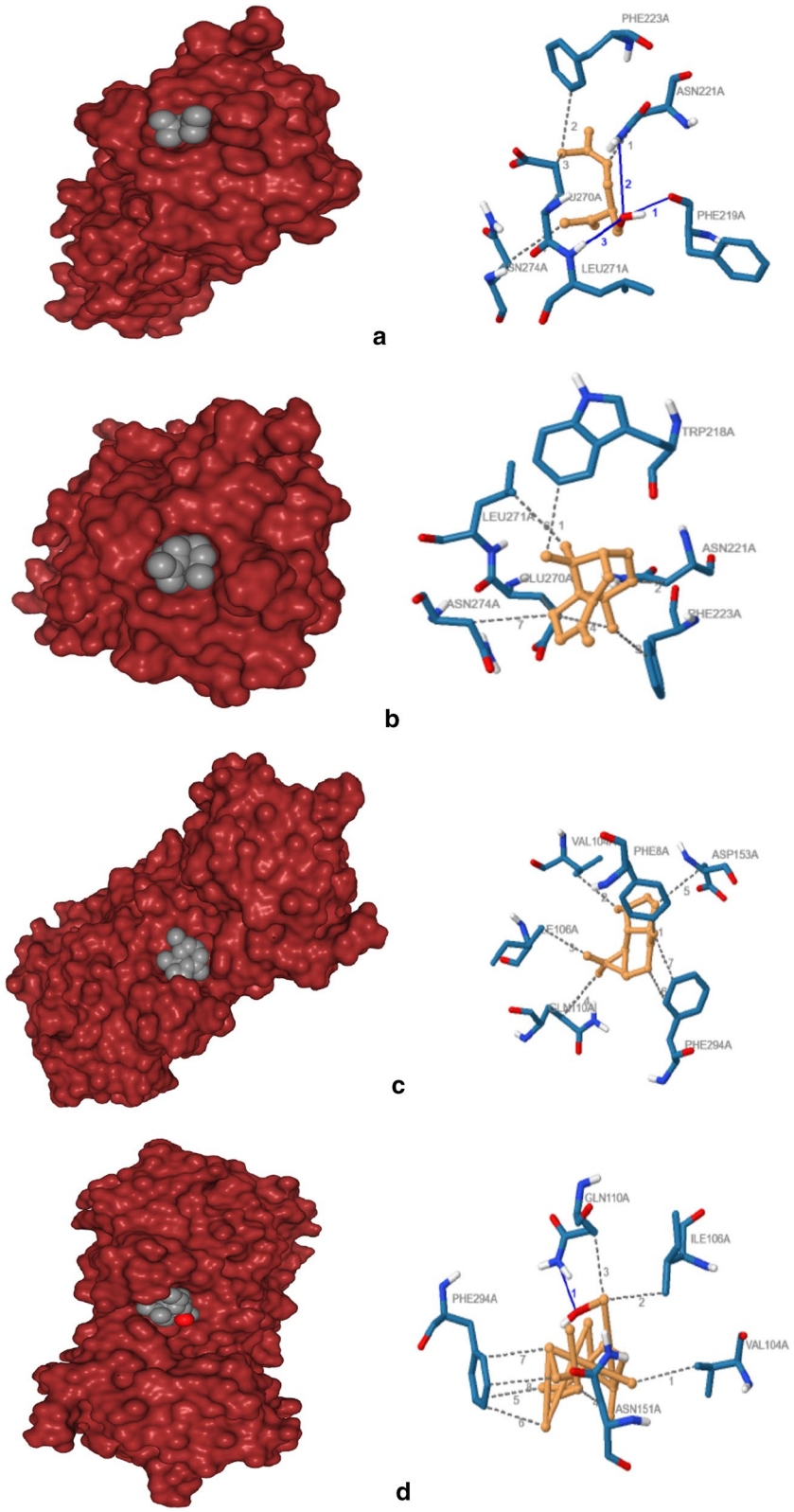

Fig. 6 The binding arrangement of Lavandulol (**a**), Cyperene (**b**), Aromadendrene (**c**), 2-Viridiflorol (**d**), Cis-Chrysanthemol (**e**) and Beta-Phellandrene (**f**) in the active site of the M^{pro} as obtained from molecular docking using AutoDock. The Protein–Ligand Interaction Profiler and Proteins Plus online service were employed to evaluate the binding interactions. Hydrogen bonds are depicted by blue dashed lines, pi stacking by green, and hydrophobic interactions by grey

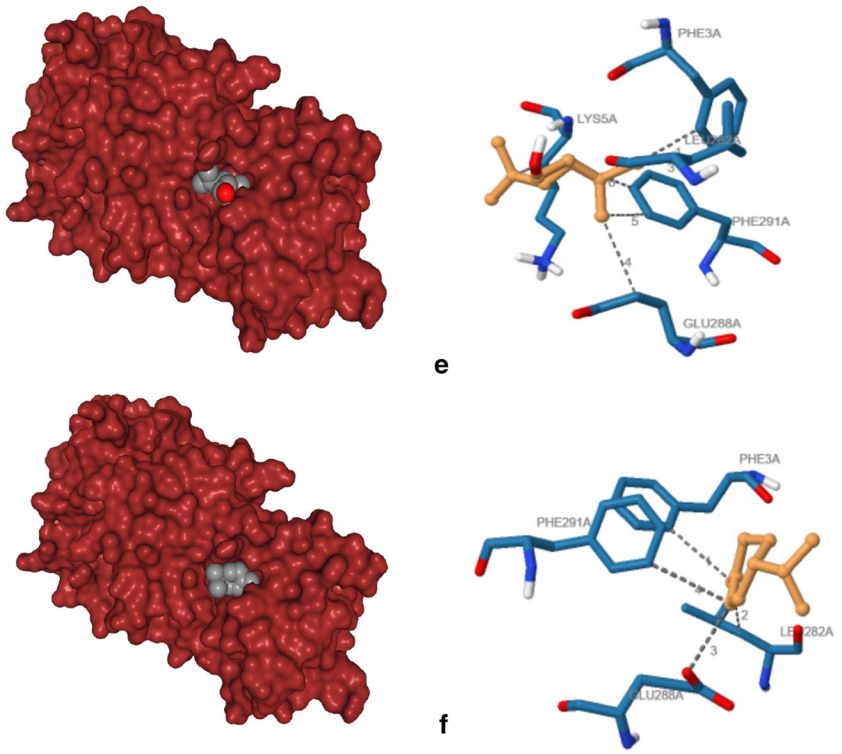

Fig. 6 continued

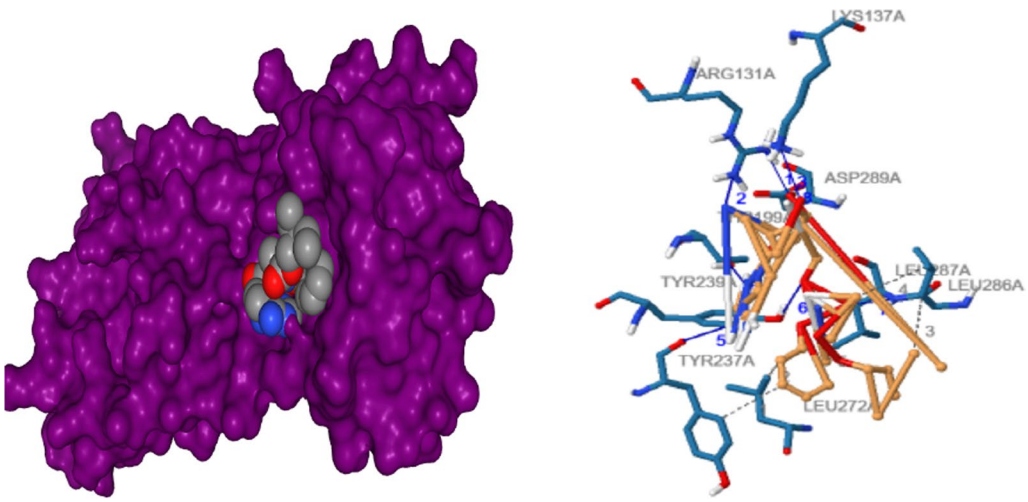

Fig. 7 The binding arrangement of Remdesivir in the active site of the M^{pro} was obtained from molecular docking using AutoDock. The Protein–Ligand Interaction Profiler and Proteins Plus online service were employed to evaluate the binding interactions. Hydrogen bonds are depicted by blue dashed lines, pi stacking by green, and hydrophobic interactions by grey

which ascertained that Gamma-Sitosterol, an extract from *Jatropha Curcas*, acts as an anti-HIV-1 and anti-SARS-CoV-2 by inhibiting reverse transcriptase of HIV-1 and proteases 3CLpro and PLpro of SARS-CoV-2. Additionally, the molecular docking study by Vincent et al. (2020) [56] revealed that Gamma-Sitosterol, a compound from *Kabasura Kudineer*, against the 3CLpro of SARS-CoV-2 with a good binding score of − 81.94. Thus, there is an urgent need for in vivo and in vitro laboratory experiments on Gamma-Sitosterol, Vitexin, Kaempferol,

Table 3 Predicted in silico ADMET properties of bioactive compounds and control drug

Class	ADMET Profile	Catechin	Epicatechin	Vitexin	Quercetin	Kaempferol	Gamma-Sitosterol	Kaur-16-ene	Remdesivir
Absorption	Caco-2 Permeability (log cm/s)	− 5.971	− 5.971	− 6.082	− 5.204	− 4.974	− 4.756	− 4.865	− 5.996
	Pgp-inhibitor	−	−	−	−	−	−	−	−
	Pgp-substrate	−	−	+	−	−	−	−	+
Distribution	Plasma protein binding	92.065%	92.065%	88.818%	95.496%	97.861%	98.314%	94.720%	46.719%
	Blood–brain barrier	−	−	−	−	−	+	+	−
Metabolism	CYP450 1A2 inhibition	−	−	−	+	+	−	−	−
	CYP450 1A2 substrate	−	−	−	−	−	−	−	−
	CYP450 3A4 inhibition	−	−	−	−	+	−	−	−
	CYP450 3A4 Substrate	−	−	−	−	−	+	+	+
	CYP450 2C9 Inhibition	−	−	−	+	+	−	−	−
	CYP450 2C9 Substrate	+	+	+	+	+	−	+	+
	CYP450 2C19 inhibition	−	−	−	−	−	−	−	−
	CYP450 2D6 Inhibition	−	−	−	−	+	−	−	+
	CYP450 2D6 Substrate	−	−	−	−	−	−	+	−
Excretion	Clearance of a drug (ml/min/kg)	17.911	17.911	3.397	8.284	6.868	16.686	9.155	3.434
Toxicity	Human ether-a-go-go inhibition	−	−	−	−	−	−	−	+
	Human Hepatotoxicity	−	−	−	−	−	−	−	+
	Ames Mutagenicity	+	+	+	+	+	−	−	+
Carcinogens	Carcinogens	−	−	−	−	−	−	−	−

BBB blood–brain barrier, PPB Plasma protein binding, CYP Cytochrome P450, + means Yes, − means No

Catechin and Epicatechin to corroborate this scholarly framework.

ADMET profiling of the hit compound specifies the pharmacokinetics feature of the compound and the efficacy of the compound on the protein target. The ADMET profile of Catechin, Epicatechin, Vitexin, Quercetin, Kaempferol, Gamma-Sitosterol, and Kaur-16-ene presented in Table 3 showed an excellent profile. Pharmacokinetics properties of compounds in Table 3 indicated that Catechin, Epicatechin, Vitexin, Quercetin, Kaempferol, Gamma-Sitosterol, and Kaur-16-ene had plasma protein binding (PPB) scores between 88 and 99%, while Remdesivir had plasma protein binding of 46.7%. A vital medication uptake and distribution mechanism is plasma protein binding (PPB). The way a medication binds to plasma proteins affects how it behaves pharmacodynamically.

PPB affects medication's oral bioavailability. The medication's free concentration is in jeopardy when it binds to serum proteins during this process. Medications are considered to have an appropriate PPB if their projected value is less than 90%, and those with high protein binding may have a lower therapeutic index [47]. Vitexin's PPB score of 88% would suggest that it has a high therapeutic index. Catechin, Epicatechin, Vitexin, Gamma-Sitosterol, and Kaur-16-ene from our research do not inhibit some key liver enzymes CYP. Cytochrome P450 (CYP) is a family of enzymes that catalyses the phase 1 metabolism of xenobiotics in general and is a crucial component of pharmacokinetics. According to Esteves et al. (2021) [57], any compound that inhibits particular isoforms will result in a medication–medication interaction. This research also predicted that the isoforms of CYP450 2C9, CYP450 2C19, CYP450 2D6, CYP450 A12, and CYP450 3A4 would not be inhibited by Catechin, Epicatechin, Vitexin, Gamma-Sitosterol, and Kaur-16-ene. Since a medication–medication interaction results in a loss of efficacy, these compounds should not inhibit

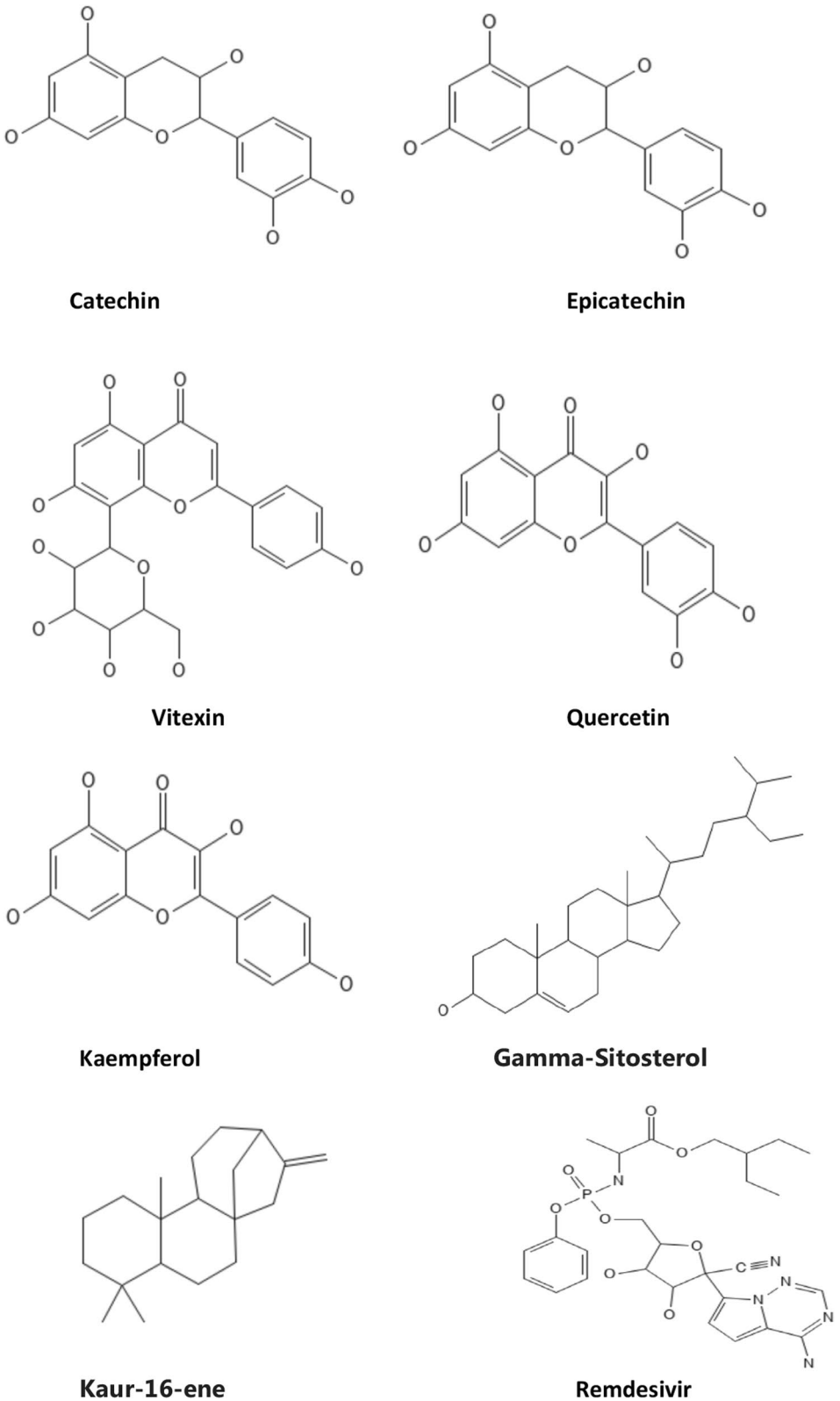

Fig. 8 2D structure of best-hit ligands and control medication [28]

these enzymes and cannot cause a medication–medication interaction.

Interestingly, all seven hit compounds were predicted to be non-carcinogenic, non-hepatotoxic and non-inhibitors to the Human-ether-a-go-go gene; this implies that the hit compounds might not be carcinogenic, cannot cause damage to the liver, and cannot affect the QT interval of the heart. However, the ADMET profile prediction also revealed that these compounds were not P-glycoprotein substrates and had higher PPB values than the control medication. The absorption and distribution defects of the bioactive compounds can be corrected by pharmacophoric modelling to improve the essential parameters of the absorption and distribution profile without affecting their binding ability and, in turn, improve their binding aptitude.

Conclusions

Our investigation revealed the twenty-three (23) compounds from the four African plants *Adansonia digitata L, Aframomum melegueta K. Schum, Ageratum conyzoides (L.), and Boswellia dalzielii Hutch* passed the Lipinski rule with zero or one violation and that indicates that they can serve as an oral medication. The molecular docking showed that Catechin, Epicatechin, Vitexin, Quercetin, and Kaempferol from *Adansonia digitata L,* Gamma-Sitosterol, from *Aframomum melegueta K. Schum* and Kaur-16-ene from *Ageratum conyzoides (L.)*, had a better binding affinity with the main protease (M^{pro}) of SARS-CoV-2 than Remdesivir. The results of this study indicated that *Adansonia digitata L, Aframomum melegueta K. Schum, and Ageratum conyzoides (L.)* might have therapeutic effects on SARS-CoV-2, while *Boswellia dalzielii* shows no therapeutic effects. With the best binding affinity, Vitexin also has a plasma protein binding below 90%, a promising medication distribution feature. These seven compounds, significantly Vitexin, may inhibit the catalytic activities of M^{pro}, thereby possessing antiviral features, which can eventually lead to the development of oral medications for COVID-19. However, there is an urgent need for molecular dynamic simulation studies as well as wet laboratory experiments to corroborate this scholarly project.

Abbreviations

SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
M^{pro}	Main protease
ADMET	Absorption, Distribution, Metabolism, Excretion, and Toxicity
COVID-19	Coronavirus Disease 2019
PDB	Protein Data Bank
PID	PubChem identification number
RCSB	Research Collaboratory of Structural Bioinformatics
SMILES	Simplified Molecular Input Line Entry System
PDBQT	Protein Data Bank, Partial Charge (Q), and Atom Type (T)
PyRx	Python prescription
BBB	Blood–brain barrier
PPB	Plasma protein binding
CYP	Cytochrome P450

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Author contributions
IAA did conceptualization, methodology, software. IAA, BOI, and OMA performed methodology, writing—original draft preparation. IAA and APO done visualization and investigation. IAA and BOI supervised the study. IAA, BOI, and OMA were involved in software and validation. IAA, BOI, OMA, and APO contributed to writing—reviewing and editing. All the authors read and approved the final version for submission.

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Availability of data and materials
We declare that all the data generated are included in this study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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